UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,549	05/02/2002	Dan L. Eaton	P3230R1C001-168	9996

20995 7590 01/18/2007

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/18/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/18/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/063,549	EATON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8-10 and 12-17* is/are rejected.

7)☒ Claim(s) *7 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment, response and declarations filed 10-20-06 has been entered into the record. Claims 1-5 have been cancelled. Claims 6-17 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

It is noted that AAY44609 is the human myocardium protein-7 of Khodadoust as represented in the databases.

Rejections Withdrawn

The rejection of claims 6-17 under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial and credible utility or, in the alternative a well-established utility is withdrawn for reasons set forth below.

The rejection of claims 6-17 under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is withdrawn for reasons set forth below.

Applicants' response states that the gene expression data in the specification, Example 18, shows that the mRNA associated with the polypeptide was more highly expressed in kidney tumor tissue as compared to normal kidney or more highly expressed in normal stomach and skin as compared to stomach or melanoma tumors. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule per se and

antibodies that specifically bind the molecule useful and enabled as a diagnostic tool for the determination of the presence or tumor.

Example 18 at page 140 of the instant specification demonstrates differential expression of DNA58850-1495 cDNA using qualitative PCR amplification reactions. DNA58850-1495 was show to be more highly expressed in esophageal and kidney tumors as compared to the corresponding normal tissue samples in this Example. Applicant states in the response that Example 18 utilizes a more accurate and reliable method of assessing changes in mRNA levels, namely quantitative PCR analysis. Applicant relies on more than 100 references, where expression levels of mRNA, measured by quantitative PCR, were found to have a good correlation to the expressed protein levels.

It had been previously argued in the office actions of record that mRNA levels were not predictive of protein levels, citing several references including Haynes et al, Gygi et al and Chen et al. However, these references were measuring and analyzing mRNA levels using microarrays, not using quantitative PCR analysis and the art recognizes the results obtained by microarray are not always the same as the results obtained using quantitative PCR (for example see Oda et al. Virchows. Arch. 430:99-105, 1997, specifically page 104, column 1, paragraph 2). While the PTO found several references in which the protein expression levels did not correlate with mRNA levels measured by quantitative PCR (see Sugg et al, Clinical Endocriniology 49:629-637, 1998; Toler et al. Am. J. Obstet. Gynecol. 194:e27-231, 2006; Berner et al Histopathol 42:546-554, 2003; Brooks et al Am. J. Renal Physiol 284:F218-F228, 2003), the majority of the references which were found, including those cited by Applicant, demonstrated a correlation between mRNA levels measured by quantitative PCR and protein expression levels.

Applicant asserts that the expression levels of protein correlate to mRNA (cDNA) levels when the cDNA is measured by quantitative PCR (i.e. rt-PCR). Applicant has provided more than 100 references in support of this position. The prior art of record (Haynes et al, Gygi et al, Chen et al.) argued by the Examiner, is not specifically directed

to message levels measured by rt-PCR. Based on the totality of evidence of record, one of skill in the art would find it more likely than not that an increase in message as measured by rt-PCR would be predictive of an increase in protein expression levels, absence evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding the polypeptide, also supports a conclusion of differential expression of the polypeptide. Therefore, one of ordinary skill in the art would be able to use the antibodies that specifically bind the polypeptide diagnostically for distinguishing tumor from normal tissue as asserted by Applicant.

All the art rejections of record are withdrawn in view of priority date of PCT US00/23328 filed 8-24-00 which has the data of Example 18 of the instant specification and the declaration filed 7-5-05 persuant 37 CFR 1.131 to obviate the potential 102(a) rejections.

Rejections Maintained

Claims 14-17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in all the office Actions of record and here.

This rejection pertains to the issue of percent identity. Applicants again argue the issue of combination of structure with function. This is again not persuasive because the "generation of an antibody that specifically detects the polypeptide of SEQ ID NO:46 " is not a function of the polypeptide per se. Applicants argue that immunological function is a function of the polypeptide. This is not persuasive because the polypeptide has no

function in regulating the immune response. It is not a cytokine or receptor that is immunoregulatory. It has no immune function. The ability to mount an immune response is not a function of the antigen, but a function of the hosts' ability to respond. As such, the ability to raise an antibody is not a function of the polypeptide, but a function of the host in which the antibody is raised. Applicants again argue Wallach. Wallach does not speak to variants of a polypeptide but nucleic acids encoding the same polypeptide. The correlation of the structure of the nucleic acid with the structure is predictable given the Wobble hypothesis. Therefore, a genus of nucleic acids encoding the same polypeptide was described. This is not the instant fact scenario. The instant case the polypeptides are different and encoded by different nucleic acids. Applicants argue that there is nothing in Example 14 of the written description guidelines that require that the function limit the structure of the variant protein in any discernable, predictable or disclose manner. This is not persuasive because the claimed function is not a function of the protein for all the reasons made of record. Applicants argue that there is nothing about the claims that require that the antibodies generated by the variant polypeptides do not bind themselves in addition to SEQ ID NO:46. If this is so.. what does the term "specifically detect SEQ ID NO:46 mean" ? Specificity is defined in The Dictionary of Immunology as "A term defining ***selective reactivity*** [emphasis added] between substances, e.g. of an antigen with its corresponding antibody or primed lymphocyte." (Herbert et al eds, The Dictionary of Immunology, Fourth Edition, Academic Press, 1995, page 147). Here, Applicants claims require that the "selectivity" not be toward the variant polypeptide that provokes the immune response in a host, but a different polypeptide. This usage of specifically binds is contrary to Applicants own use of "specific" in the specification as it relates to antibodies at [0366] which teaches that '... is typically immunized with an immunizing antigen to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent.". Immunological activity is set forth in the specification as the ability to induce the production of an antibody against an antigen epitope possessed by a

native or naturally-occurring PRO. This paragraph in context with [0366] conveys to the skilled artisan the ability to raise "specifically binding antibodies" against itself, when itself is used as an immunogen and not variant peptides. The specification as filed does not describe a variant polypeptide that generates an antibody that specifically binds a different polypeptide. The specification does not describe variants with the claimed property. The genus encompasses antibodies that specifically detect SEQ ID NO:46 polypeptide wherein the immunizing polypeptides have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes. However, the present specification fails to provide sufficient disclosure of such polypeptides that maintain the structural and functional properties of the claimed limitation of specifically detecting SEQ ID NO:46 in esophageal or kidney tissue samples. The specification does not provide sufficient guidance as to which of the amino acids may be changed while 'claimed antigen specificity" structural or functional activity and specificity is retained. Furthermore, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document) and Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). As such, in the absence of the description of a representative number of species of polypeptides that fall within the genus and have the recited property, the skilled artisan would readily appreciate that the disclosure of a single SEQ ID NO did not place Applicants in possession of the now claimed genus at the time of filing.

Claims 6, 8 and 12-17 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons made of record in the office actions of record.

Applicants argues that the standard for definiteness does not require that the particular structure of the signal sequence be defined in the claims because the claims are read in light of the specification. This argument is not persuasive, the claim read in light of the specification at page 119, paragraph [0441] teach that various polypeptide-encoding nucleic acid sequences were identified by applying a **proprietary** signal sequence finding algorithm developed by Genetech, Inc.. The algorithm is not described in the specification. The skilled artisan would not be readily apprised of the specifics used to determine signal sequences. This passage does not provide the metes and bounds of any signal polypeptide *per se*. In fact, a review of the figures indicates that the signal sequences disclosed are different lengths and structures and therefore, in the absence of a precise delineation in the claims, the metes and bounds of any signal sequence is insoluably indefinite, especially in that a admittedly proprietary algorithm was used to identify such. The skilled artisan in this art is not readily apprised of admitted proprietary information and algorithms. As such, the metes and bounds of the "signal sequence" is *prima facie* indefinite and limitations from the specification or figure are not read into the claims.

Claims 14-17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons made of record in the office action mailed 1-5-06 and herein.

This rejection pertains to the issue of new matter in view of the wherein phrase of the independent claims 14 and 15. Applicants argue that cross-reactive antibodies are contemplated by the specification as filed. This is not persuasive, the relied upon passage does not provide for the concept in the claims. Applicants argue that there is nothing

about the claims that require that the antibodies generated by the variant polypeptides do not bind themselves in addition to SEQ ID NO:46. If this is so.. what does the term "specifically detect SEQ ID NO:46 mean" ? Specificity is defined in The Dictionary of Immunology as "A term defining ***selective reactivity*** [emphasis added] between substances, e.g. of an antigen with its corresponding antibody or primed lymphocyte." (Herbert et al eds, The Dictionary of Immunology, Fourth Edition, Academic Press, 1995, page 147). Here, Applicants claims require that the "selectivity" not be toward the variant polypeptide that provokes the immune response in a host, but a different polypeptide. This usage of specifically binds is contrary to Applicants own use of "specific" in the specification as it relates to antibodies at [0366] which teaches that '... is typically immunized with an immunizing antigen to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent.". Immunological activity is set forth in the specification as the ability to induce the production of an antibody against an antigen epitope possessed by a native or naturally-occurring PRO. This paragraph in context with [0366] conveys to the skilled artisan the ability to raise "specifically binding antibodies" against itself, when itself is used as an immunogen and not variant peptides.

Status of Claims

Claims 7 and 11 are objected to as depending from a rejected base claim. Claims 6, 8-10 and 12-17 are rejected.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Jeffrey Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Pat a. Duffy

Patricia A. Duffy

Primary Examiner

Art Unit 1645